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REVIEW ARTICLES

Role of Platelets in Restenosis After Percutaneous Coronary Revascularization

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The role of platelets in the process of restenosis after percutaneous coronary intervention is not fully understood. After vascular injury there is extensive platelet activation, adhesion, aggregation and secretion. Through the liberation of growth factors, such as platelet-derived growth factor, and surface expression of cell adhesion molecules, such as the glycoprotein IIb/IIIa integrin, platelets appear to be a pivotal mediator of the vascular injury response. Experimental models have demonstrated that profound, prolonged thrombocytopenia, or blockade of the IIb/IIIa receptor, may reduce neointimal hyperplasia after arterial balloon injury. However, multiple clinical trials testing conventional or new platelet agents have not yielded any salutary effects. The recent finding that abciximab, a monoclonal antibody fragment directed against IIb/IIIa, reduced clinical restenosis after coronary angioplasty by 26% in patients raises questions about the mechanism of benefit. The $\alpha_v\beta_3$ vitronectin receptor is responsible for binding endothelial cells to platelets, and it also has a key role in modulating smooth muscle cell migration. It is possible that the antibody fragment exerts its effect on restenosis by means of $\alpha_v\beta_3$, because abciximab fully cross-reacts to this integrin owing to the shared β_3 subunit. To date, the other platelet glycoprotein IIb/IIIa inhibitors, including Integrelin, Tirofiban, Lamifiban and Xemilofiban, are specific in binding to this particular integrin. Considerable further study is necessary to unravel the effects of platelets on the restenosis process.

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Restenosis after percutaneous coronary intervention, initially recognized nearly 20 years ago (1), remains the main limitation of the technique (2–6). A large number of clinical trials testing pharmacologic approaches have failed to reduce the incidence of ~30% to 40% of patients with significant angiographic recurrence. There has been unexpected difficulty in deriving clinical therapeutic interventions from agents demonstrated to be effective in experimental models. Recently, the first significant pharmacologic-mediated reduction in clinical restenosis in the human was reported (7). The drug was a monoclonal antibody fragment, and its target was the platelet glycoprotein IIb/IIIa receptor. The purpose of this review is to discuss the role of platelets in intimal hyperplasia and the potential of these cells as a therapeutic target to reduce restenosis.

Role of Platelets in Intimal Hyperplasia

Balloon angioplasty disrupts the continuity of the endothelium and induces deep arterial injury, exposing the subendothelium to the blood. The injury sets up key adhesive interactions between cells and their ligands. The circulating "resting" platelets can recognize adhesive substrates and rapidly adhere to the damaged surface. The adhesive response of platelets represents an initial step, which may be followed by platelet secretion and aggregation (8). Platelet secretion results in the local release of intracellular granule constituents, including diphosphate, serotonin, thromboxane A_2, fibrinogen, fibronectin and von Willebrand factor (vWF). These substances contribute to the activation of neighboring platelets and induce aggregation and thrombus formation. Other released substances include chemokines and mitogens such as platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-beta) and basic fibroblast growth factor (b-FGF). These growth factors stimulate the migration and proliferation of smooth muscle cells (8,9), which are considered to be pivotal to the formation of a neointimal lesion. When a PDGF neutralizing antibody was administered to rats subjected to balloon carotid injury (10), the development of an intimal lesion was inhibited by 40%, predominantly by inhibition of smooth muscle cell migration. Infusion of b-FGF for 8 h in the same animal model was followed by increased smooth muscle cell replication 24 to 48 h later (11), and an antibody to b-FGF suppressed this response (12). Recently, an in vitro experiment confirmed that platelets, or growth factors (PDGF, b-FGF, epidermal growth factor, interleukin-1) alone or in combination, stimulated proliferation of human coronary smooth muscle cells derived from atherectomized restenotic lesions (13). Furthermore, in vivo data from the porcine injury model also

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Abbreviations and Acronyms

b-FGF	=	basic fibroblast growth factor
EPIC	=	Evaluation of IIb/IIIa Platelet Receptor Antagonist 7E3 in Preventing Ischemic Complications trial
EPILOG	=	Evaluation of PTCA to Improve Long-Term Outcome by 7E3 GPIIb/IIIa Receptor Blockade trial
GP	=	glycoprotein
IMPACT II	=	Integrelin to Minimize Platelet Aggregation and Coronary Thrombosis, phase II trial
KGD	=	Lys-Gly-Asp sequence
PDGF	=	platelet-derived growth factor
RGD	=	Arg-Gly-Asp sequence
TGF-beta	=	transforming growth factor-beta
vWF	=	von Willebrand factor

emphasize the importance of PDGF for the effect of interleukin-1-beta on promoting intimal hyperplasia (14).

Platelet deposition occurs immediately after the arterial injury, but the time during which active platelet accumulation continues is species dependent (15–17). The degree of platelet deposition and thrombosis is determined mainly by the degree of arterial wall injury (18,19), but also by the transport of platelets to the injured area (20). Platelet transport is largely determined by the wall shear rate. Abnormally high shear stress, such as that which occurs in stenosed arteries, can activate and aggregate platelets in the absence of exogenous agonists (21–24). Thus, in the context of coronary angioplasty, if a significant residual stenosis remains, platelet deposition may be increased because of elevated shear stress at the site of the lesion (25,26).

Experimental Studies Implicating Platelets in Restenosis

In 1977, the important role of platelets in restenosis was highlighted by Friedman et al. (27) in a thrombocytopenic animal study. Thrombocytopenia was induced in rabbits and maintained until their death by daily injections of antiplatelet serum to maintain a daily platelet count $<7{,}000/cm^3$. The abdominal aorta and right iliac arteries were denuded of endothelium by a balloon catheter. The prolonged, severe thrombocytopenia was found to inhibit neointimal formation after balloon injury. Rabbits given the antibody 2 to 3 days before the injury failed to develop intimal thickening. As an extension of this finding, the inhibition of intimal hyperplasia was related to the degree of thrombocytopenia. Sustained thrombocytopenic levels $<7{,}000/cm^3$ were necessary to inhibit neointimal formation. Of note, the extent of re-endothelialization, as assessed by Evans blue stain, was not affected by the extent of thrombocytopenia. Fingerle et al. (17) subsequently confirmed in a rat model that the absence of platelets at the site of injury inhibited formation of intimal lesions, although neither the time of onset nor the extent of smooth muscle cell replication was affected. The main mechanism appeared to be through inhibition of smooth muscle cell migration. In this study, thrombocytopenia was also induced by an antiplatelet antibody and was severe at the time of the injury (<1% of normal platelet count). By 48 h, platelet counts had significantly increased and were normal by 96 h. The size of intimal lesions at 4 and 7 days were significantly reduced as compared with control rats, but by 14 days the intimal areas were the same for both groups. When the animals were kept thrombocytopenic for an observation period of 7 days, no intimal lesions were present.

Induction of thrombocytopenia is an impractical clinical approach to prevent restenosis. Thus, agents that block platelet activation have been tested. It has been shown in animal studies that platelet deposition at the site of balloon injury can be significantly reduced by pretreatment with antiplatelet agents. In the pig model, there is a significant reduction with pretreatment with aspirin alone or aspirin combined with dipyridamole (19). In a rabbit model, the intravenous administration of aspirin or a thromboxane synthetase inhibitor was similarly effective in reducing platelet deposition after angioplasty (28).

Only a few animal studies have tested the effect of generalized antiplatelet therapy on restenosis. Two studies (29,30), using the same rabbit model of atherosclerosis, examined the effect of a combination of aspirin and dipyridamole administered orally. The treatment was introduced 1 or 2 days before angioplasty and maintained until the time of death. In one study, antiplatelet drugs significantly reduced the incidence of restenosis (29), whereas in the second study (30) this regimen was ineffective despite an almost total inhibition of platelet aggregation to collagen.

Early Clinical Trials

Early clinical trials failed to demonstrate any beneficial effect of antiplatelet agents on restenosis after coronary angioplasty, although the acute complications were significantly reduced. Schwartz et al. (31) evaluated the role of high dose aspirin (330 mg three times daily, introduced 24 h before coronary angioplasty) with dipyridamole in reducing the rate of restenosis in patients after successful angioplasty. The use of this antiplatelet regimen did not reduce the 6-month rate of restenosis, but it markedly reduced the incidence of periprocedural myocardial infarction (1.6% in the treated group vs. 6.9% in the placebo group) (31). These data were confirmed by another study using the same combination, aspirin (975 mg/day) with dipyridamole (225 mg/day) (32). Ticlopidine, another platelet inhibitor, was also ineffective in reducing restenosis at a dose of 250 mg twice daily, compared with aspirin/dipyridamole and placebo (33,34). Serruys et al. (35) tested a potent and specific thromboxane A_2 receptor blocking drug in a randomized, placebo-controlled trial. At follow-up, the loss of minimal lumen diameter was identical in the control and treated groups, despite a 90% reduction of platelet aggregation through the thromboxane A_2 pathway in the treated group. Another trial confirmed that either selective thromboxane A_2 receptor antagonism with Sulotroban or

nonselective thromboxane A_2 receptor antagonism with aspirin had no effect on the rate of angiographically detected restenosis at 6 months after coronary angioplasty (36,37).

There are several potential explanations for why these clinical trials have failed to demonstrate the ability of antiplatelet agents to prevent restenosis after coronary angioplasty. First, there are no data to substantiate a reduction of platelet accumulation at the site of injury (16). Numerous platelet agonists, including thrombin, collagen, adenosine diphosphate and high shear, can stimulate platelets even in the face of aspirin therapy (38). Second, even a major reduction in the aggregation response of platelets may be insufficient to prevent a substantial release of the chemokines involved in the initiation of the proliferative response. Factors released from other cell types (injured endothelial cells, injured medial smooth muscle cells or white blood cells) may play an important role. Third, these antiplatelet agents have negligible effects on platelet adhesion.

Thus, the failure of the antiplatelet agents tested in clinical trials should not lead to the conclusion that platelets are not involved in restenosis or are an inappropriate therapeutic target. In the last decade, platelet membrane receptors involved in fundamental aspects of platelet adhesion and aggregation have been identified and have been candidate targets for more effective antiplatelet therapy. These new agents are already under investigation in experimental studies and in clinical trials. First we briefly describe the platelet receptors, and then we update the status of in vivo studies, testing the blocking of these receptors to limit the vascular injury response.

Platelet Membrane Receptors

The platelet membrane receptors have been the subject of recent reviews (39–43). It was the detection of specific abnormalities in platelets isolated from patients with inherited disorders of platelet aggregation (Glanzman's thrombasthenia) and adhesion (Bernard-Soulier syndrome) that provided the first real clue that membrane glycoproteins were essential to platelet functions (44). These functions include platelet attachment to a diverse number of extracellular matrix proteins, including vWF, collagen, fibronectin and laminin. In particular, the promiscuous ability of glycoprotein (GP) IIb-IIIa complexes to bind fibrinogen and other adhesive proteins is a key to hemostasis. Table 1 summarizes some of the essential functions of the platelet membrane glycoproteins. Several of them are involved in adhesion with a main role for the GP Ib-IX complexes.

Adhesion receptors. Platelet adhesion is a multistep process in which attachment is followed by activation and spreading on the exposed surface. The platelets adhere only when the endothelial surface is interrupted, exposing the subendothelial substrates such as collagen, vWF, fibronectin, vitronectin and laminin. The major receptors involved have been identified.

GP Ib is present in the platelet membrane in a tight complex with a low molecular weight component, GP IX (45,46). About 25,000 copies are found on unstimulated platelets (45). GP Ib-IX complexes mediate the adhesion of unstimulated platelets to vWF bound within the subendothelium of damaged vessels. In particular, they anchor the platelets to the subendothelium under high shear conditions. Attachment of platelets to vWF leads to activation, granule secretion and platelet aggregation (23,47). Moreover, GP Ib has at least one binding site to alpha thrombin and there is some evidence linking GP Ib to platelet activation by thrombin (48).

Table 1. Major Glycoprotein Receptors Involved in Platelet Adhesion and Aggregation

Receptors	Ligand	Function
Leucin-rich protein: Ib-IX	vWF, thrombin	Adhesion
Integrins		
Ia-IIa ($\alpha_2\beta_1$)	Collagen	Adhesion
Ic-IIa ($\alpha_5\beta_1$)	Fibronectin	Adhesion
Ic′-IIa ($\alpha_6\beta_1$)	Laminin	Adhesion
IIb-IIIa ($\alpha_{2b}\beta_3$)	Fibrinogen, vWF, fibronectin, vitronectin	Aggregation
VnR ($\alpha_v\beta_3$)	Vitronectin, fibrinogen, vWF	?

VnR = vitronectin receptor; vWF = von Willebrand factor.

Although platelet attachment to subendothelium depends primarily on the GP Ib–vWF interaction, other platelet receptors are also involved, including the integrins. The integrins constitute a widespread family of receptors that mediate many cell–cell and cell–substratum interactions (48–50). All integrins are heterodimers of alpha and beta subunits. Platelets contain five integrins, two of the β_3 subfamily ($\alpha_{IIb}\beta_3$, $\alpha_v\beta_3$) and three of the β_1 subfamily ($\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$) (51). The $\alpha_2\beta_1$ receptor (GP Ia-IIa complex) is a universal receptor for type I collagen that is the most thrombogenic macromolecular constituent in the subendothelium and that not only serves as an effective substrate for platelet adhesion, but is also a potent initiator of platelet aggregation. The $\alpha_5\beta_1$ (GP Ic-IIa complex) plays a role in platelet adhesion to fibronectin and the $\alpha_6\beta_1$ (GP Ic′-IIa complex) in platelet adhesion to laminin. The exact role of the various β_1 integrins in platelet adhesion in vivo remains to be evaluated.

Aggregation receptors. Activation of the GP IIb-IIIa receptor is the final common pathway involved in platelet aggregation (42). Binding studies with monoclonal antibodies reveal ~50,000 to 75,000 copies of GP IIb-IIIa on each rest platelet. When platelets are stimulated with physiologic agonists, GP IIb-IIIa undergoes a conformational change that enables it to bind fibrinogen. It was established that other adhesive proteins are also able to bind to activated GP IIb-IIIa. These include vWF, fibronectin and vitronectin. These interactions are mediated by Arg-Gly-Asp sequences (RGD) within these ligands. Although fibrinogen can bind to GP IIb-IIIa by its RGD sequences, an amino acid sequence located at the carboxy-terminus of the gamma chain is primarily involved in its binding to GP IIb-IIIa (52). RGD containing peptides and gamma chain peptides are inhibitors of the binding of fibrinogen to activated GP IIb-IIIa (53,54).

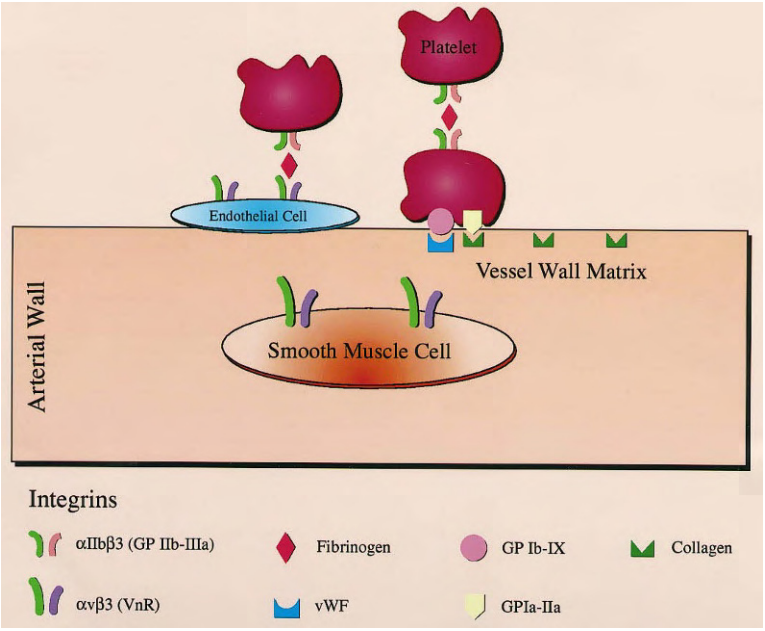

Figure 1. Schematic representation of the main receptors involved in platelet adhesion and aggregation. Several of the different molecules involved in the various cell–cell interactions discussed can have multiple ligands (e.g. vWF has distinct sites for both GP Ib and GP IIb/IIIa).

Fibrinogen binding to activated GP IIb-IIIa complexes is thought to mediate aggregation by binding platelets together (Fig. 1) (55). As in platelet adhesion, shear rate also plays a role in platelet aggregation. At high shear rates, the aggregation may be more dependent on vWF than on fibrinogen (22). With distinct and different binding sites for GP Ib and IIb-IIIa, vWF may actively participate in both platelet adhesion and aggregation.

The $\alpha_v\beta_3$ Integrin

Platelets express two β_3 receptors, not only $\alpha_{IIb}\beta_3$ (GP IIb-IIIa), but also $\alpha_v\beta_3$ (vitronectin receptor). Although $\alpha_v\beta_3$ is present in platelets, it is a minor component. Studies with $\alpha_v\beta_3$ specific monoclonal antibodies suggest that as few as 50 molecules are expressed on the platelet surface (56,57). The α_v and α_{IIb} subunits have 36% sequence identity (58). In humans, GP IIb-IIIa complexes are confined to platelets and cells of the megakaryocyte lineage, whereas $\alpha_v\beta_3$ is heavily expressed by numerous cells, including endothelial cells, monocytes, smooth muscle cells and melanoma cells (59–63). Although the functional role of platelet $\alpha_v\beta_3$ has not been established, the $\alpha_v\beta_3$ integrin is thought to play a major role in the adhesion and migration of smooth muscle cells and endothelial cells on extracellular matrix, and consequently in the restenotic process. This integrin appears to bind several extracellular matrix proteins (vitronectin, fibronectin, thrombospondin, laminin, collagen I and IV), and antiserum against this receptor inhibits smooth muscle cell migration on all substrates (64). Moreover, $\alpha_v\beta_3$ binds osteopontin, another matrix protein, whose role was recently described (65–67). Osteopontin promotes adhesion and migration of both vascular smooth muscle cells and endothelial cells through an RGD-mediated interaction (65–67). An antibody against $\alpha_v\beta_3$ partially inhibits smooth muscle cell and endothelial cell adhesion and migration to osteopontin. Vitronectin-induced human aortic smooth muscle cell migration is also mediated, at least in part, by the $\alpha_v\beta_3$ receptor (60). Moreover, $\alpha_v\beta_3$ appears to mediate endothelial cell spreading and migration (68) and might promote the survival of endothelial cells after the arterial injury and the regrowth of the monolayer (67). In addition, it might be possible for both a platelet and an endothelial cell to bind the same fibrinogen molecule through their β_3 integrins—$\alpha_{IIb}\beta_3$ and $\alpha_v\beta_3$, respectively (Fig. 1) (69). This additional mechanism for platelet adhesion may play a role in the restenosis process.

Glycoprotein IIb-IIIa Antagonists

A series of compounds—antibodies, peptides and small molecules—has been developed to antagonize GP IIb-IIIa function. These compounds have been shown to be much more effective than aspirin in animal models of thrombosis and have considerable promise in cardiovascular medicine, as discussed in recent reviews (70,71). Several of these compounds have undergone preliminary evaluations in humans and are under investigation in large clinical trials.

Monoclonal antibody. The first platelet fibrinogen receptor blocker tested in patients was a murine monoclonal antibody known as 7E3 (Centocor) developed by Coller (72). The antibody preparation has been substantially modified over time. As originally developed, the monoclonal antibody 7E3 was entirely murine in composition. Because of concern about immunogenicity, a chimeric monoclonal 7E3 Fab (c7E3 Fab) was created by means of genetic reconstruction. This new

molecule consists of the variable region derived from the original murine protein (imparting specificity to the integrin GP IIb-IIIa) hybridized with the remaining human constant region of the Fab fragment of an immunoglobulin G molecule.

Chimeric 7E3 (abciximab) appears to be considerably more effective than current antiplatelet agents in preventing platelet aggregation. Turner et al. (73) recently reported that under flow conditions of abnormally increased shear stress analogous to those in narrowed coronary arteries (in vitro study), the in vivo injection of c7E3 Fab, in contrast to heparin or aspirin, markedly reduced platelet aggregate formation mediated by the binding of fibrinogen and vWF to platelet GP IIb-IIIa.

The pharmacodynamic properties of c7E3 Fab were elucidated during phase II clinical investigations and have been previously described (74). Chimeric 7E3 Fab produces a dose-dependent blockade of platelet GP IIb-IIIa receptors, which is correlated with inhibition of the platelet aggregatory response. Platelet function, evaluated by measurements of platelet aggregation, GP IIb-IIIa blockade and bleeding time began to recover within 6 h of the cessation of infusion. These variables do not completely return to normal for at least 2 to 4 days. Reversion of normal platelet aggregation is dependent on new platelets released into the circulation. Another recent study investigated the effects on ex vivo shear-induced platelet aggregation of c7E3 Fab administered to patients undergoing coronary angioplasty (75). The results confirm that c7E3 Fab injection results in a rapid, extensive blockade of GP IIb-IIIa receptors (98%) and a 50% inhibition of ex vivo platelet aggregation induced by shear stress. Partial reversibility of the inhibition was noted within 2 days after drug administration (still 30% inhibition), but even after 1 week, platelet function had not been fully restored. Thus, a potential limitation of the antibody is an increased bleeding risk. In contrast, the protracted effect on platelet function may highlight a distinct advantage.

Peptides and peptidomimetics. The peptidomimetics and peptides have two theoretical advantages over 7E3. First, there is a reduced risk of immunogenicity, although the clinical importance of this phenomenon in the case of c7E3 Fab remains to be established. Second, many of these compounds have a shorter duration of action, implying that adverse effects might be more manageable by cessation of the infusion. Moreover, another advantage is the oral bioavailability of some of those molecules. Several synthetic peptides have been developed (76–81), including cyclic RGD peptides and Integrelin (COR Therapeutics), a cyclic KGD (Lys-Gly-Asp) heptapeptide actively under investigation in clinical trials. This latter peptide may be an even more specific inhibitor of GP IIb-IIIa than RGD-containing peptides. Moreover, RGD derivatives (modification of the RGD sequence to improve stability and activity) and peptidomimetics have been designed (82–98). Two peptidomimetics, Tirofiban (MK-383) and Lamifiban (Ro-44 9883), have already been studied in phase II clinical trials and are currently being assessed in phase III trials of unstable angina.

Experience With Glycoprotein Antagonists in Restenosis

Glycoprotein IIb-IIIa antagonists. *Experimental studies.* The effect of GP IIb-IIIa antagonists in preventing the response to vascular injury has been examined in several animal studies. Azrin et al. (99) tested in a rabbit model of balloon angioplasty an antibody (AZ-1) that binds to the rabbit platelet GP IIb-IIIa receptor and inhibits platelet function both in vitro and in vivo. The rabbits were randomized to receive a single bolus of placebo 20 min before angioplasty, a single bolus of AZ-1 or two boluses of AZ-1 given 3 days apart. After a single bolus, platelet aggregation remained abnormal (initially >80% inhibition) for 72 h. Two intermittent boluses achieved platelet inhibition for longer than 6 days. With respect to intimal area or minimal lumen diameter, however, there were no significant differences between the AZ-1 antibody-treated and control groups 4 weeks after angioplasty. With the intermittent dosing, it is possible that the GP IIb-IIIa blockade was not sustained long enough to prevent the intimal hyperplasia. Alternatively, injection of foreign intact antibody may have induced an immunologic response, as suggested by the investigators (99), that had counterbalancing effects on the response to vascular injury in this rabbit model of atherosclerosis.

In contrast to this negative study, Matsuno et al. (80), using a hamster carotid artery model of restenosis, demonstrated that a nonspecific RGD peptide (G4120, Genentech, Inc.), an inhibitor of both integrins $\alpha_{IIb}\beta_3$ and $\alpha_v\beta_3$, inhibited neointima hyperplasia in a dose-dependent fashion, when administered for the complete observation period. A shorter treatment period (<7 days) was not effective, indicating that integrin inhibition is needed beyond the first few days. This late beneficial effect may be related to the inhibition of smooth muscle cell $\alpha_v\beta_3$ receptors.

Clinical trials. In the Evaluation of IIb/IIIa Platelet Receptor Antagonist 7E3 in Preventing Ischemic Complications (EPIC) trial (100) the chimeric 7E3 monoclonal antibody (abciximab) was tested in 2,099 patients undergoing high risk coronary interventions with unstable angina, recent or evolving myocardial infarction or high risk angiographic morphology. Patients were clinically followed up for at least 6 months to determine the need for repeat revascularization and the occurrence of ischemic events (7). At 6 months, there was a 23% reduction in the rate of major ischemic events or elective repeat coronary revascularization in the treated group compared with the placebo group when abciximab was administered as a bolus followed by a 12-h intravenous infusion (Fig. 2). The bolus-only group had an intermediate outcome that was not significantly better than that of the placebo group.

The EPIC study was the first clinical trial to demonstrate that platelet aggregation inhibition sustained for at least 36 to 48 h after the procedure was associated with a reduced rate of clinical restenosis. However, there are some limitations that do not permit definitive conclusions. First, no systematic angiographic follow-up at 6 months was performed to confirm the mechanistic effect. Another large-scale trial of abciximab

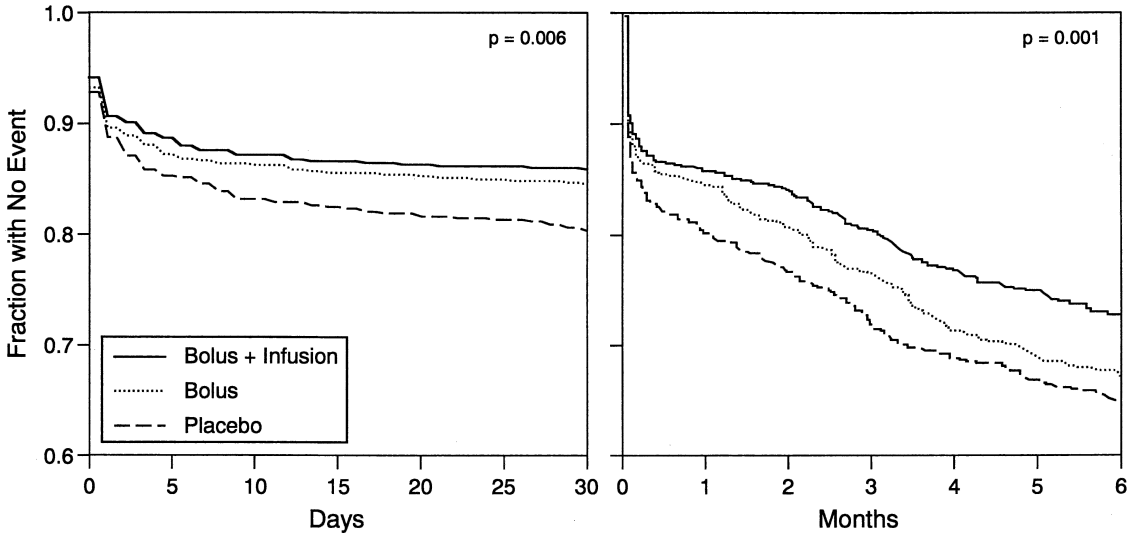

Figure 2. Event-free survival of patients at 30 days and 6 months in the EPIC trial (7,100). (**Right panel** adapted from Topol et al. [7], with permission.)

for restenosis, which includes systematic angiographic follow-up, is currently ongoing (Evaluation of PTCA to Improve Long-Term Outcome by c7E3 GP IIb/IIIa Receptor Blockade [EPILOG]). Second, because $\alpha_v\beta_3$ is very closely related to $\alpha_{IIb}\beta_3$ by virtue of its common beta subunit, abciximab fully cross reacts with $\alpha_v\beta_3$, as do certain peptides and peptidomimetics (101). Thus, the beneficial effect of c7E3 could be related to the blockade of $\alpha_v\beta_3$ rather than GP IIb/IIIa, or the blockade of both receptors may be necessary.

The benefit of selectively blocking GP IIb/IIIa was assessed in another large clinical trial (Integrelin to Minimize Platelet Aggregation and Coronary Thrombosis [IMPACT II]) involving 4,010 patients with Integrelin, which has marked specificity for GP IIb/IIIa. This trial included three treatment groups, a placebo group and two Integrelin groups. Each of the two Integrelin groups received 135 mg/kg body weight bolus followed by a 20-h infusion of 0.5 mg/kg ("low dose") or 0.75 mg/kg ("high dose"). Patients were followed clinically at 30 days and angiographically at 6 months in a subset of 918 patients. At 30 days, there was a trend toward a reduction in end points (death, myocardial infarction, repeat urgent or emergency percutaneous coronary intervention or coronary artery bypass surgery) in the treated groups (11.4% in placebo, 9.2% Integrelin low dose, 9.9% Integrelin high dose), but the results were not statistically significant. In the angiographic substudy, the rates of restenosis at 6 months, defined by >50% diameter restenosis, were not significantly different in the three groups. Thus, according to these results, a 20-h blockade of the GP IIb-IIIa receptor with a specific antagonist does not prevent restenosis after coronary angioplasty. Possible explanations include a lack of adequate duration of the GP IIb-IIIa effect, inadequate dosing for maximal inhibition of platelet aggregation or specificity of the GP IIb-IIIa effect. It may be necessary, in light of our current knowledge of the integrin $\alpha_v\beta_3$, to also achieve its blockade and avoid specificity to GP IIb-IIIa.

***$\alpha_v\beta_3$* antagonists.** The potential therapeutic benefit of $\alpha_v\beta_3$ blockade has been reported by Choi et al. (102). In an in vitro assay, a monoclonal antibody to human $\alpha_v\beta_3$ inhibited the migration of human aortic smooth muscle cells. However, this inhibition was not complete, and other integrins probably play a role in smooth muscle cell motility. A cyclic RGD peptide antagonist of $\alpha_v\beta_3$ (GpenGRGDSPCA, Telios Pharmaceuticals) has a similar inhibitory effect on human and rabbit smooth muscle cell migration. The same investigators also tested the effects of the local administration of this RGD peptide in a rabbit model of balloon carotid artery injury. The agent, delivered locally through a microcatheter connected to an osmotic pump until the time of sacrifice (2 weeks), prevented neointimal formation by 70%. The same peptide locally applied to the carotid artery through an adventitial pluronic gel in rats led to a 92% reduction in hyperplasia after injury (103). These results were confirmed by those of Lundgren et al. (104), who also applied an $\alpha_v\beta_3$ antagonist (a cyclic RGD peptide) by use of a gel, after carotid balloon injury in the rabbit model. At 28 days, there was a significant decrease (76%) in the mean intima/media ratio in the treated group compared with the control group.

Glycoprotein Ib antagonists. Like the $\alpha_v\beta_3$ antagonists, the GP Ib antagonists have only been tested in experimental studies. VCL, an antagonist of the von Willebrand–GP Ib binding domain, inhibits botrocetin and ristocetin GP Ib–dependent platelet agglutination (105), inhibits platelet adhesion at the site of arterial injury and reduces platelet deposition in a rat model of arterial thrombosis (106). In a recent study, Zahger et al. (107), using a rat model of femoral artery injury, confirmed that VCL profoundly decreased platelet deposition at the site of balloon injury. This effect was associated with a significant reduction of the intimal thickening. The agent was

administered as an intravenous bolus 15 min before the injury, followed by continuous intravenous administration by an infusion pump for 3 days. Platelet adhesion reductions of 83% and 88% were observed at 1 day and 3 days, respectively. At 14 days, there was a 60% reduction in the intima media ratio. Because no effect was observed on smooth muscle cell proliferation, the mechanism was presumed to be an inhibition of cell migration or matrix deposition.

Conclusions

Platelets play an important role in the restenosis process after balloon angioplasty. Early experimental studies highlighted this role. Thrombocytopenia inhibits the intimal hyperplasia after arterial injury, provided it is established well before the time of injury and is sustained. Previous experimental studies and clinical trials testing antiplatelet drugs have been disappointing, suggesting that new and more powerful agents, such as the GP IIb/IIIa antagonists, may be required. These agents represent new hope to reduce restenosis after coronary angioplasty, as suggested by 6 months of follow-up in the EPIC study. Nevertheless, important questions remain to be answered. Blockade of only the GP IIb/IIIa receptor for a limited period (<36 h) may be not sufficient, as suggested by the results of the IMPACT II angiographic substudy. Further investigation will be necessary to determine whether other receptors, especially $\alpha_v\beta_3$ alone or in combination with GP IIb/IIIa antagonists, are critical in preventing restenosis.

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